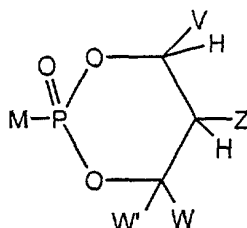


1. A method of enhancing oral bioavailability of a parent drug by administering to an animal a prodrug of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$,
 $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$,
 $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,
 $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and
 5 $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or

10 alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically
 15 active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or
 nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

2. The method of claim 1 wherein M is attached to the phosphorus in formula I via
 20 an oxygen atom or a carbon atom.

3. The methods of claim 2 wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl,
 substituted aryl, heteroaryl, and substituted heteroaryl, or

25 together V and W are connected via an additional 3 carbon atoms to form an optionally
 substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected
 from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and
 aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached
 to the phosphorus;

30 together Z and W are connected via an additional 3-5 atoms to form a cyclic group,
 optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or
 substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$,
 $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$,
 $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,
 $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and
 5 $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H or alkyl;

10 R^2 is selected from the group consisting of R^3 and -H;

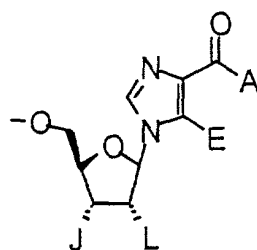
R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl; and

R^{12} is selected from the group consisting of -H, and lower acyl.

4. The method of claim 3 wherein MH is selected from the group consisting of araA,

15 AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro
 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine,
 TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC,
 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC.
 araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT,
 20 tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6
 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9
 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy
 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza
 2'deoxyctidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene
 25 {PMEA, PMEDAP, HPMPC, HPMPA, FPMPA, PMPA, foscarnet, and phosphonoformic acid.}

5. The method of claim 3 wherein M is a compound of formula II:



II

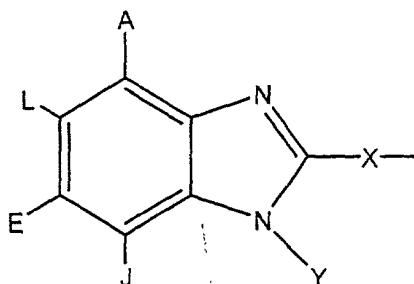
wherein

E is selected from the group consisting of alkyl, amino or halogen;

L and J are independently selected from the group consisting of hydrogen, hydroxy, acyloxy, alkoxycarbonyloxy, or when taken together form a lower cyclic ring containing at least one oxygen; and

A is selected from the group consisting of amino and lower alkylamino; and pharmaceutically acceptable salts thereof.

6. The method of claim 3 wherein M is a compound of formula IV:



wherein:

A, E, and L are selected from the group consisting of $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidine, amidine, $-NHSO_2R^5$, $-SO_2NR^4_2$, $-CN$, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group including aryl, cyclic alkyl, and heterocyclic;

J is selected from the group consisting of $-NR^8_2$, $-NO_2$, $-H$, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, $-CN$, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl,

haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with O forms a cyclic group including aryl, cyclic alkyl and heterocyclic alkyl;

X is selected from the group consisting of alkylamino, alkyl(hydroxy), alkyl(carboxyl), alkyl(phosphonate), alkyl, alkenyl, alkynyl, alkyl(sulfonate), aryl, carbonylalkyl, 1,1-

5 dihaloalkyl, alkylaminoalkyl, alkoxyalkyl, alkylthioalkyl, alkylthio, alkylaminocarbonyl, alkylcarbonylamino, alicyclic, aralkyl, and alkylaryl, all optionally substituted; or together with O forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

O is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-OR^3$,

10 $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except -H are optionally substituted; or together with X forms a cyclic group including aryl, cyclic alkyl, and heterocyclic;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, and lower aryl;

15 R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

20 R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, -OH, $-NH_2$ and $-OR^3$; and

25 pharmaceutically acceptable prodrugs and salts thereof; with the provisos that:

a) when X is alkyl or alkene, then A is $-NR^8_2$;

b) X is not alkylamine and alkylaminoalkyl when an alkyl moiety is substituted with phosphonic esters and acids; and

c) A, L, E, J, O, and X together may only form 0-2 cyclic groups.

7. The method of claim 1 wherein MPO_3^{2-} , $\text{MP}_2\text{O}_6^{3-}$, or $\text{MP}_3\text{O}_9^{4-}$ is useful for the treatment of diseases of the liver or metabolic diseases where the liver is responsible for the overproduction of a biochemical end product.

8. The method of claim 7 wherein said disease of the liver is selected from the group consisting of hepatitis, cancer, fibrosis, malaria, gallstones, and chronic cholecystalithiasis.

9. The methods of claim 8 wherein MPO_3^{2-} , $\text{MP}_2\text{O}_6^{3-}$, or $\text{MP}_3\text{O}_9^{4-}$ is an antiviral or anticancer agent.

10. The method of claim 7 wherein said metabolic disease is selected from the group consisting of diabetes, atherosclerosis, and obesity.

11. The method of claim 7 wherein said biochemical end product is selected from the group consisting of glucose, cholesterol, fatty acids, and triglycerides.

12. The method of claim 11 wherein MPO_3^{2-} is an AMP activated protein kinase activator.

13. The method of claim 1 wherein M-PO_3^{2-} is a compound that inhibits human liver FBPase.

14. The method of claim 13 wherein said compound inhibits human liver FBPase with an IC_{50} of less than $10 \mu\text{M}$.

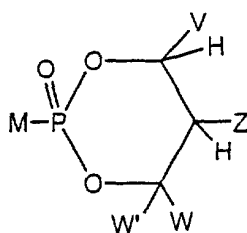
15. The method of claim 1 wherein said oral bioavailability is at least 5%.

16. The method of claim 15 wherein said oral bioavailability is at least 10%.

17. The method of claim 15 wherein said oral bioavailability is enhanced by 50% compared to the parent drug administered orally.

18. The method of claim 16 wherein said oral bioavailability is enhanced by at least 100%.

5 19. A method of delivering a biologically active drug to an animal for a sustained period using compounds of formula I:



I

wherein:

10 V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

15 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

20 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkylthio, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

25 together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

5 Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p\text{-OR}^{12}$, and $-(\text{CH}_2)_p\text{-SR}^{12}$;

p is an integer 2 or 3;

10 with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

15 R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

20 and pharmaceutically acceptable prodrugs and salts thereof.

20. The method of claim 19 wherein M is attached to the phosphorus in formula I via an oxygen atom or a carbon atom.

25 21. The methods of claim 20 wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

30 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$,
 5 $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$,
 $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,
 $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and
 $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H or alkyl;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl.

22. The method of claim 21 wherein MH is selected from the group consisting of
 araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro
 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine,
 20 TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC,
 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC,
 araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT,
 tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6
 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9
 25 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy
 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza
 2'deoxyctidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene
 PMEA, PMEDAP, HPMPC, HPMPA, FPMPA, PMPA, foscarnet, and phosphonoformic acid.

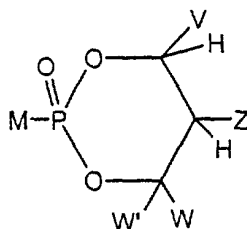
23. The method of claim 19 whereby therapeutic levels of said drug are maintained
 for at least one hour longer than the levels achieved by oral administration of the
 bispivaloyloxymethyl (bis-POM) ester.

24. The method of claim 19 whereby therapeutic levels of said FBPase inhibitors are maintained for at least one hour longer after systemic administration relative to an equivalent molar amount of the parent compound administered by the same route.

25. The method of claim 19 wherein MPO_3^{2-} is an FBPase inhibitor.

26. The method of claim 19 wherein MH or MPO_3^{2-} is an antiviral or anticancer agent.

27. A method of delivering a biologically active drug to an animal with greater selectivity for the liver using compounds of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,

alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and

aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

28. The method of claim 27 wherein M is attached to the phosphorus in formula I via an oxygen atom or a carbon atom.

29. The methods of claim 28 wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H or alkyl;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl.

30. The method of claim 29 wherein MH is selected from the group consisting of araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC, araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycophormycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxyctidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene

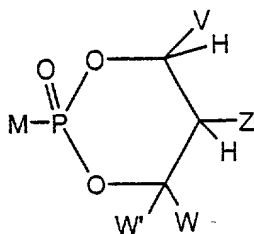
PMEA, PMEDAP, HPMPC, HPMPA, FPMMA, PMPA, foscarnet, and phosphonoformic acid.

31. The method of claim 27 whereby the ratio of a parent drug or a drug metabolite concentration in the liver over a parent drug or a drug metabolite concentration in the plasma is two times greater compared to administration of a parent drug.

32. The method of claim 31 wherein the liver specificity has increased relative to administration of $M-PO_3^{2-}$.

33. The method of claim 27 wherein said biologically active drug is a triphosphate generated in the liver.

34. A method of increasing the therapeutic index of a drug by administering to an animal compounds of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}=\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p\text{-OR}^{12}$, and $-(\text{CH}_2)_p\text{-SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

35. The method of claim 34 wherein M is attached to the phosphorus in formula I via an oxygen atom or a carbon atom.

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

p is an integer 2 or 3;

with the provisos that:

20

a) V, Z, W, W' are not all -H; and

b) when Z is -R², then at least one of V, W, and W' is not -H or alkyl;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R¹² is selected from the group consisting of -H, and lower acyl.

SD-128854.1

(arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxycytidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene PMEA, PMEDAP, HPMPC, HPMPA, FPMMPA, PMPA, foscarnet, and phosphonoformic acid.

5

38. The method of claim 34 wherein extrahepatic toxicity is reduced.

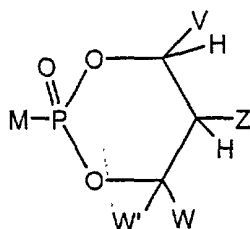
39. The method of claim 38 wherein $M-PO_3^{2-}$ is excreted by the kidney.

40. The method of claim 38 wherein the M is selected from the group consisting of PMEA, PMEDAP, HPMPA, FPMMPA, and PMPA.

41. The method of claim 38 wherein the gastrointestinal toxicity is reduced.

42. The method of claim 38 wherein central or peripheral nervous system toxicity is reduced.

43. A method of bypassing drug resistance by administering to an animal compounds



of formula I:

I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

44. The method of claim 43 wherein M is attached to the phosphorus in formula I via an oxygen atom or a carbon atom.

45. The methods of claim 44 wherein

5 V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

15 Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

20 p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H or alkyl;

R^2 is selected from the group consisting of R^3 and -H;

25 R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl.

46. The method of claim 45 wherein MH is selected from the group consisting of araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC,

araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxycytidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene (PMEA, PMEDAP, HPMPC, HPMPA, FMPMPA, PMPA, foscarnet, and phosphonoformic acid}

47. The method of claim 43 wherein said resistance arises from decreased cellular production of $M-PO_3^{2-}$.

48. The method of claim 43 wherein said compound is an anticancer or antiviral agent.

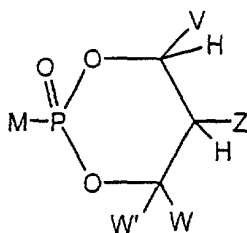
49. The method of claim 48 wherein M is 5-fluoro-2'-deoxyuridine.

50. The method of claim 48 wherein said resistance is to an antiviral agent selected from the group consisting of araA, AZT, d4T, 3TC, ribavirin, 5 fluoro-2'deoxyuridine, FMAU, DAPD, FTC, 5-yl-carbocyclic 2'deoxyguanosine, Cyclobut G, dFdC, araC, IDU, FaraA, ACV, GCV, and penciclovir.

51. The method of claim 48 wherein the resistance or lack of antihepatitis activity is due to a deficiency in thymidine kinase and said antiviral agent is selected from the group consisting of AZT, d4T, and ACV.

52. The method of claim 48 wherein said anticancer agent is selected from the group consisting of dFdC, araC, F-araA, and CdA.

53. A method of treating cancer by administering to an animal a compound of formula I:



I

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,

$-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
- b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

54. The method of claim 53 wherein M is attached to the phosphorus in formula I via an oxygen atom or a carbon atom.

55. The methods of claim 54 wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,

$-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H or alkyl;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl.

56. The method of claim 55 wherein MH is selected from the group consisting of araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC, araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxycytidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene PMEA, PMEDAP, HPMPC, HPMPA, FMPMA, PMPA, foscarnet, and phosphonoformic acid.

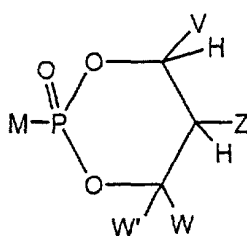
57. The method of claim 53 wherein the active drug is the triphosphate of M-H.

58. The method of claim 53 wherein the active drug is the monophosphate of M-H.

59. The method of claim 53 wherein MH is selected from the group consisting of dFdC, araC, FaraA, CdA, 5-fluoro 2'deoxyuridine, GCV, tiazofurin, IDU, 5,6 dihydro-5-azacytidine, 5-azacytidine, and 5-aza 2'deoxycytidine.

60. The method of claim 59 wherein MH is selected from the group consisting of dFdC, araC, FaraA, CdA, and 5-fluoro 2'deoxyuridine.

61. A method of treating viral infections by administering to an animal a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkylthio, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

5 Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}=\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

10 with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

15 R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

20 and pharmaceutically acceptable prodrugs and salts thereof.

62. The method of claim 61 wherein M is attached to the phosphorus in formula I via an oxygen atom or a carbon atom.

25 63. The methods of claim 62 wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or

30 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, carbonyloxy, alkylthiocarbonyloxy, and aryloxy, carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H or alkyl;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl.

64. The method of claim 63 wherein MH is selected from the group consisting of araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FLAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC, araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycophorylmycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxyctidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cyallene PMEA, PMEDAP, HPMPC, HPMPA, FPMPA, PMPA, foscarnet, and phosphonoformic acid.

65. The method of claim 61 wherein said viral infection is hepatitis.

66. The method of claim 65 wherein said hepatitis is hepatitis B.

67. The methods of claim 61 wherein viral kinases produce $M-PO_3^{2-}$.

68. The method of claim 61 wherein said viral infection is hepatitis and said viral
5 kinases are kinases from viruses other than the hepatitis viruses.

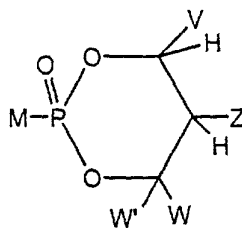
69. The method of claim 61 wherein the active drug is the triphosphate of M-H.

70. The method of claim 61 wherein MH is selected from the group consisting of
10 araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, FIAU, FIAC, L-FMAU, TFT, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl carbocyclic 2'deoxyguanosine, cytallene, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, araT, ACV, GCV, penciclovir, PMEA, PMEDAP, HPMPC, HPMPA, PMPA, and foscarnet.

71. The method of claim 70 wherein MH is selected from the group consisting of
15 3TC, penciclovir, FMAU, DAPD, FTC, Cyclobut G, ACV, GCV, PMEA, HPMPA, 5-yl-carbocyclic 2'deoxyguanosine, and ribavirin.

72. The method of claim 71 wherein MH is selected from the group consisting of
20 dFdC, araC, FaraA, CdA, 5-fluoro 2'deoxyuridine, GCV, tiazofurin, IDU, 5,6 dihydro-5-azacytidine, 5-azacytidine, and 5-aza 2'deoxycytidine.

73. A method of treating liver fibrosis by administering to an animal a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy,

5 alkoxy-carbonyloxy, or aryloxy-carbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

10 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy-carbonyloxy, alkylthio-carbonyloxy, and aryloxy-carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

15 together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or 20 substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and 25 $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or

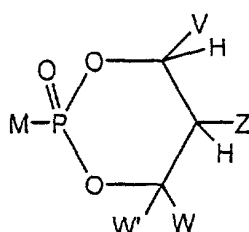
30 alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

74. A method of treating hyperlipidemia by administering to an animal a compound of formula I:



I

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

5 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p\text{-OR}^{12}$, and $-(\text{CH}_2)_p\text{-SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

15 a) V, Z, W, W' are not all -H; and
b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

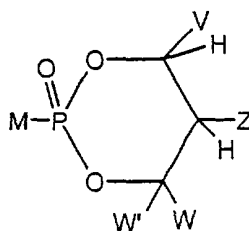
R^{12} is selected from the group consisting of -H, and lower acyl;

20 M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

25 75. The method of claim 74 wherein the hyperlipidemia agent is a squalene synthase inhibitor.

76. A method of treating parasitic infections by administering to an animal a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

R^2 is selected from the group consisting of R^3 and $-H$;

5 R¹² is selected from the group consisting of -H, and lower acyl;

and pharmaceutically acceptable prodrugs and salts thereof.

Chemical structure I is a six-membered ring containing two oxygen atoms and a phosphorus atom (P=O). The ring is substituted with groups V, H, Z, H, W, and W'.

15 V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, carbonyloxy, or aryloxy, carbonyloxy attached to a carbon atom that is three atoms from
20 both O groups attached to the phosphorus; or

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

5 together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- 15 a) V, Z, W, W' are not all -H; and
b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

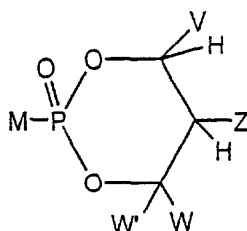
20 M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

25 78. The method of claim 77 wherein MH is IDU.

79. A method of making a prodrug of a compound drug having a $-\text{PO}_3^{2-}$ moiety comprising,

- a) transforming said phosph(on)ate into a compound of formula I:



I

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,

$-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

- 5 a) V, Z, W, W' are not all -H; and
b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

10 R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

15 80. The method of claim 79 further comprising,

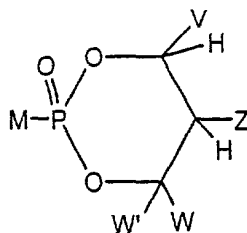
- a) converting M-PO_3^{2-} to a compound $\text{M-P(O)L}''_2$ wherein L'' is a leaving group selected from the group consisting of halogen; and
b) reacting $\text{M-P(O)L}''_2$ with $\text{HO-CH(V)CH(Z)CH(Z)-CW(W')-OH}$.

20 81. The method of claim 80 wherein $\text{HO-CH(V)CH(Z)-CW(W')-OH}$ is a single stereoisomer.

25 82. The method of claim 81 further comprising isolating a single diastereomer.

83. A method of making a prodrug of formula I by

- a) converting a hydroxyl or amino or MH to a phosph(oramid)ite by reaction with $\text{L-P(-OCH(V)CH(Z)-CW(W')O-)}$ wherein L selected from the group consisting of NR^1_2 , and halogen;
30 b) transforming said phosph(oramid)ite into a compound of formula I by reaction with an oxidizing agent, wherein



I

wherein:

- 5 V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, alkoxy, or aryloxy, attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or
- 10 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;
- 15 together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxy, alkoxy, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;
- 20 together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;
- 25 Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2_2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,

$-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

5 a) V, Z, W, W' are not all -H; and
b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

10 R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

and pharmaceutically acceptable prodrugs and salts thereof.

15 84. The method of claim 83 wherein $\text{L-P}(-\text{OCH}(\text{V})\text{CH}(\text{Z})-\text{CW}(\text{W}')\text{O}-)$ is a single stereoisomer.

20 85. The method of claim 83 further comprising isolating a single diastereomer of said phosph(oramid)ite, $\text{M-P}(-\text{OCH}(\text{V})\text{CH}(\text{Z})-\text{CWW-O}-)$.

86. The method of claim 84 wherein said oxidizing agent produces a major stereoisomer at the phosphorus in a ratio of at least 3:1.

25 87. The method of making a prodrug of formula I comprising converting a hydroxyl or an amino to a phosphate or phosphoramidate, respectively, by reaction with $\text{L}'-\text{P}(\text{O})(-\text{OCH}(\text{V})\text{CH}(\text{Z})-\text{CW}(\text{W}')\text{O}-)$ wherein L' is a leaving group selected from the group consisting of $-\text{NR}_2$, aryloxy, and halogen.

30 88. The method of claim 87 wherein $\text{L}'-\text{P}(\text{O})(-\text{OCH}(\text{V})\text{CH}(\text{Z})-\text{CW}(\text{W}')\text{O}-)$ is a single stereoisomer.

90. The method of claim 79 further comprising the step of reacting $M-PO_3^{2-}$ with a coupling reagent and $HO-CH(V)CH(Z)CWW'OH$.

92. The method of claim 91, wherein HO-CH(V)CH(Z)CWW'OH is a single stereoisomer.

$$R^1_2N-P-(-OCH(V)CH(Z)-CW(W')O-)$$

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxy, carbonyloxy, or aryloxy, carbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

5 Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

10 with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

15 R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R^{12} is selected from the group consisting of -H, and lower acyl;

M is selected from the group that attached to PO_3^{2-} , $\text{P}_2\text{O}_6^{3-}$, or $\text{P}_3\text{O}_9^{4-}$ is a biologically active agent, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom;

20 and pharmaceutically acceptable prodrugs and salts thereof.

each R^1 is independently selected from the group consisting of alkyl, aryl, and aralkyl;

or together R^1 and R^1 form a cyclic group, optionally containing a heteroatom;

with the proviso that both R^1 groups are not benzyl or ethyl at the same time.

25 94. A compound $\text{R}^1_2\text{N}-\text{P}(\text{O})(-\text{OCH}(\text{V})\text{CH}(\text{Z})-\text{CW}(\text{W}')\text{O}-)$

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or

30 together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$, $-\text{OCOR}^3$, $-\text{OCO}_2\text{R}^3$, $-\text{SCOR}^3$, $-\text{SCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-\text{CH}_2\text{NHaryl}$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and $-(\text{CH}_2)_p-\text{SR}^{12}$;

p is an integer 2 or 3;

with the provisos that:

a) V, Z, W, W' are not all -H; and

b) when Z is $-\text{R}^2$, then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

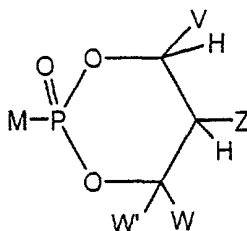
R^{12} is selected from the group consisting of -H, and lower acyl;

each R^1 is independently selected from the group consisting of alkyl, aryl, and aralkyl;

or together R^1 and R^1 form a cyclic group, optionally containing a heteroatom;

with the proviso that both R^1 groups are not benzyl or ethyl at the same time.

95. A compound of formula I:



1

wherein:

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl; or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally 1 heteroatom, substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxy carbonyloxy attached to a carbon atom that is three atoms from both O groups attached to the phosphorus; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma position to the O attached to the phosphorus;

together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy, attached to one of said carbon atoms that is three atoms from an O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-\text{CHR}^2\text{OH}$, $-\text{CHR}^2\text{OC}(\text{O})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{R}^3$, $-\text{CHR}^2\text{OC}(\text{S})\text{OR}^3$, $-\text{CHR}^2\text{OC}(\text{O})\text{SR}^3$, $-\text{CHR}^2\text{OCO}_2\text{R}^3$, $-\text{OR}^2$, $-\text{SR}^2$, $-\text{CHR}^2\text{N}_3$, $-\text{CH}_2\text{aryl}$, $-\text{CH}(\text{aryl})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2_2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, $-\text{R}^2$, $-\text{NR}^2_2$,

-OCOR³, -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl, -(CH₂)_p-OR¹², and -(CH₂)_p-SR¹²;

p is an integer 2 or 3;

with the provisos that:

- 5 a) V, Z, W, W' are not all -H; and
b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

M is selected from the group that attached to PO₃²⁻, P₂O₆³⁻, or P₃O₉⁴⁻ is a biologically active agent and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or
10 nitrogen atom with the proviso that M-PO₃²⁻ is not an FBPase inhibitor;
and pharmaceutically acceptable prodrugs and salts thereof.

96. The compounds of claim 95 wherein MPO₃²⁻, MP₂O₆³⁻, and MP₃O₉⁴⁻ is selected from the group consisting of an antiviral, anticancer, anti-fibrotic, antihyperlipidemic, anti-
15 diabetic, and antiparasitic agents.

97. The compound of claim 95 wherein MPO₃²⁻, MP₂O₆³⁻, and MP₃O₉⁴⁻ is selected from the group consisting of metalloprotease inhibitor, and TS inhibitor.

20 98. The method of claim 3 wherein MH is selected from the group consisting of araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC,
25 araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza
30 2'deoxycytidine, AICAR, ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, cytallene PMEA, PMEDAP, HPMPC, HPMPA, FPMMPA, PMPA, foscarnet, and phosphonoformic acid.

99. The compounds of claim 96 wherein MH is selected from the group consisting of ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, and cytallene.

100. The compounds of claim 95 wherein M^{MP02-} is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMPA, FPMMPA, and PMPA.

101. The compounds of claim 95 wherein $M-PO_3^{2-}$ is selected from the group consisting of phosphonoformic acid, and phosphonoacetic acid.

102. The compounds of claim 95 wherein

V, W, and W' are independently selected from the group consisting of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl, or together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxy carbonyloxy, attached to one of said carbon atoms that is three atoms from a O attached to the phosphorus;

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2aryl$, $-CH(aryl)OH$, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^{12}$, and $-(CH_2)_p-SR^{12}$;

p is an integer 2 or 3;

with the provisos that:

- a) V, Z, W, W' are not all -H; and
b) when Z is -R², then at least one of V, W, and W' is not -H, alkyl, aralkyl, or alicyclic;

R² is selected from the group consisting of R³ and -H;

5 R³ is selected from the group consisting of alkyl, aryl, alicyclic, and aralkyl;

R¹² is selected from the group consisting of -H, and lower acyl;

103. The compounds of claim 102 wherein V is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl; or

10 together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, that is fused to an aryl group attached at the beta and gamma position to the O attached to the phosphorus;

or together V and W are connected via an additional 3 carbon atoms to form a cyclic substituted group containing 6 carbon atoms and mono-substituted with a substituent selected
15 from the group consisting of hydroxyl, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy attached to one of said additional carbon atoms that is three atoms from an O attached to the phosphorus.

104. The compounds of claim 103 wherein V is selected from the group consisting of
20 aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

105. The compounds of claim 104 wherein Z, W, and W' are H.

106. The compounds of claim 106 wherein V is selected from the group consisting of
25 aryl and substituted aryl.

107. The compounds of claim 106 wherein V is selected from the group consisting of phenyl, and substituted phenyl.

30 108. The compounds of claim 107 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, and 3-bromophenyl.

109. The compounds of claim 108 wherein V is selected from the group consisting of heteroaryl and substituted heteroaryl.

110. The compounds of claim 109 wherein V is 4-pyridyl.

111. The compounds of claim 103 wherein together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, that is fused to an aryl group at the beta and gamma positions to the O attached to phosphorus.

112. The compounds of claim 111 wherein said aryl group is an optionally substituted monocyclic aryl group and the connection between Z and the gamma position of the aryl group is selected from the group consisting of O, CH₂, CH₂ CH₂, OCH₂ or CH₂O.

113. The compounds of claim 103 wherein together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and mono-substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy attached to one of said additional carbon atoms that is three atoms from an O attached to the phosphorus.

114. The compounds of claim 113 wherein together V and W form a cyclic group selected from the group consisting of -CH₂-CH(OH)-CH₂-, -CH₂CH(OCOR³)-CH₂-, and -CH₂CH(OCO₂R³)-CH₂-.

115. The compounds of claim 102 wherein V is -H, and Z is selected from the group consisting of -CHR²OH, -CHR²OCOR³, and -CHR²OCO₂R³.

116. The compounds of claim 104 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, and 4-pyridyl;

Z is selected from the group consisting of -OR², -SR², -CHR²N₃, -R², -NR²₂, -OCOR², -OCO₂R³, -SCOR³, -SCO₂R³, -NHCOR², -NHCO₂R³, -CH₂NHaryl, -(CH₂)_p-OR¹², and -(CH₂)_p-SR¹².

117. The compounds of claim 116 wherein Z is selected from the group consisting of $-\text{OR}^2$, $-\text{R}^2$, $-\text{OCOR}^2$, $-\text{OCO}_2\text{R}^3$, $-\text{NHCOR}^2$, $-\text{NHCO}_2\text{R}^3$, $-(\text{CH}_2)_p-\text{OR}^{12}$, and, $-(\text{CH}_2)_p-\text{SR}^{12}$.

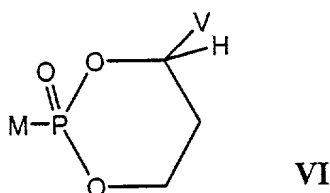
118. The compounds of claim 117 wherein Z is selected from the group consisting of $-\text{OR}^2$, $-\text{H}$, $-\text{OCOR}^2$, $-\text{OCO}_2\text{R}^3$, and $-\text{NHCOR}^2$.

119. The compounds of claim 104 wherein W and W' are independently selected from the group consisting of H, R^3 , aryl, substituted aryl, heteroaryl, and substituted aryl.

120. The compounds of claim 119 wherein W and W' are the same group.

121. The compounds of claim 120 wherein W and W' are H, or $-\text{CH}_3$.

122. The compounds of claim 104 wherein said prodrug is a compound of formula VI:



wherein

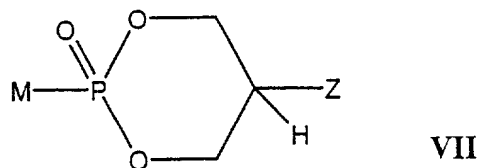
V is selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

123. The compounds of claim 122 wherein M is attached to phosphorus via an oxygen or nitrogen atom.

124. The compounds of claim 122 wherein V is selected from the group consisting of phenyl and substituted phenyl.

125. The compounds of claim 123 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, and 4-pyridyl.

126. The compounds of claim 102 wherein said prodrug is a compound of formula VII:



wherein

Z is selected from the group consisting of:

-CHR²OH, -CHR²OC(O)R³, -CHR²OC(S)R³, -CHR²OCO₂R³, -CHR²OC(O)SR³,
-CHR²OC(S)OR³, -SR², and -CH₂aryl.

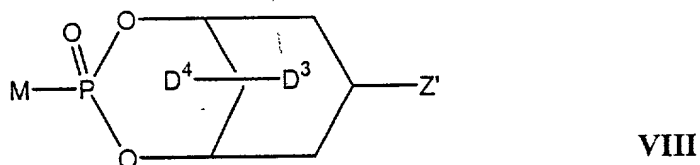
127. The compounds of claim 126 wherein M is attached to the phosphorus via a nitrogen or oxygen atom.

128. The compounds of claim 127 wherein Z is selected from the group consisting of -CHR²OH, -CHR²OC(O)R³, and -CHR²OCO₂R³.

129. The compounds of claim 128 wherein R² is -H.

130. The compounds of claim 102 wherein said prodrug is a compound of formula

VIII:



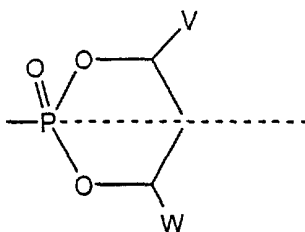
wherein

Z' is selected from the group consisting of -OH, -OC(O)R³, -OCO₂R³, and -OC(O)SR³;

D³ and D⁴ are independently selected from the group consisting of -H, alkyl, -OH, and -OC(O)R³.

131. The compounds of claim 130 wherein D³ and D⁴ are -H.

132. The compounds of claim 102 wherein W' and Z are -H, W and V are both the same aryl, substituted aryl, heteroaryl, or substituted heteroaryl such that the phosphonate prodrug moiety:



has a plane of symmetry.

133. The compounds of claim 102 wherein W and W' are H, V is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, and Z is selected from the group consisting of -H, OR², and -NHCOR².

134. The compounds of claim 133 wherein Z is -H.

135. The compounds of claim 102 wherein phosphorus is attached to an oxygen in a primary hydroxyl group on M.

136. The compounds of claim 135 wherein V is selected from the group consisting of phenyl or substituted phenyl.

137. The compounds of claim 136 wherein V is selected from the group consisting of 3,5-dichlorophenyl, 3-bromo-4-fluorophenyl, 3-chlorophenyl, and 3-bromophenyl.

138. The compounds of claim 135 wherein V is an optionally substituted monocyclic heteroaryl containing at least one nitrogen atom.

139. The compounds of claim 138 wherein V is 4-pyridyl.

140. The compounds of claims 122, 126, or 130 wherein MH is selected from the group consisting of araA, AZT, d4T, ddI, ddA, ddC, L-ddC, L FddC, L-d4C, L-Fd4C, 3TC, ribavirin, 5-fluoro 2'deoxyuridine, FIAU, FIAC, BHCG, L FMAU, BvaraU, E-5-(2-bromovinyl-2' deoxyuridine, TFT, 5-propynyl-1 arabinosyluracil, CDG, DAPD, FDOC, d4C, DXG, FEAU, 5 FLG, FLT, FTC, 5-yl-carbocyclic 2'deoxyguanosine, oxetanocin A, oxetanocin G, Cyclobut A, Cyclobut G, dFdC, araC, bromodeoxyuridine, IDU, CdA, FaraA, Coformycin, 2'-deoxycoformycin, araT, tiazofurin, ddAPR, 9-(arabinofuranosyl)-2,6 diaminopurine, 9-(2'-deoxyribofuranosyl)-2,6 diaminopurine, 9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine, 9 (arabinofuranosyl)guanine, 9-(2' deoxyribofuranosyl)guanine, 9-(2'-deoxy 2'fluororibofuranosyl)guanine, FMdC, 5,6 dihydro-5-azacytidine, 5-azacytidine, 5-aza 2'deoxycytidine, and AICAR.

141. The compounds of claims 122, 126, or 130 wherein MH is selected from the group consisting of ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, and cyttallene.

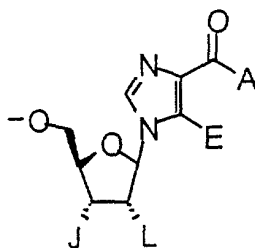
142. The compounds of claims 122, 126, or 130 wherein M is attached to the phosphorus via a carbon atom.

143. The compounds of claims 122, 126, or 130 wherein MPO_3^{2-} is selected from the group consisting of phosphonoformic acid, and phosphonoacetic acid.

144. The compounds of claims 122, 126, or 130 wherein $[MH]^{MPO_3^{2-}}$ is selected from the group consisting of PMEA, PMEDAP, HPMPC, HPMPA, FPMMPA, and PMPA.

145. The compounds of claim 122 wherein V is selected from the group consisting of phenyl substituted with 1-3 halogens and 4-pyridyl, and MH is selected from the group consisting of araA, AZT, d4T, 3TC, ribavirin, 5 fluoro-2'deoxyuridine, FMAU, DAPD, FTC, 5-yl-carbocyclic 2'deoxyguanosine, Cyclobut G, dFdC, araC, IDU, FaraA, ACV, GCV, and penciclovir, [PMEA, HPMPC, and HPMPA].

146. The compounds of claims 122, 126, or 130 wherein M is selected from the group consisting of:



II

wherein

E is selected from the group consisting of alkyl, amino or halogen;

L and J are independently selected from the group consisting of hydrogen, hydroxy,
5 acyloxy, alkoxy carbonyloxy, or when taken together form a lower cyclic ring containing at least one oxygen; and

A is selected from the group consisting of amino and lower alkylamino; and
pharmaceutically acceptable prodrugs and salts thereof.

10 147. The compounds of claims 95 wherein MH is an acyclic nucleoside.

148. The compounds of claim 147 wherein MH is selected from the group consisting of ACV, GCV, penciclovir, (R)-9-(3,4 dihydroxybutyl)guanine, and cytallene.

15 149. The compounds of claim 148 wherein MH is selected from the group consisting of ACV, GCV, and penciclovir.

150. The compounds of claim 95 wherein MH is a dideoxy nucleoside.

20 151. The compounds of claim 150 wherein MH is selected from the group consisting of AZT, d4T, ddI, ddA, ddC, L-ddC, L-FddC, L d4C, L-Fd4C, d4C, and ddAPR.

152. The compounds of claim 151 wherein MH is selected from the group consisting of AZT, d4T, ddI, and ddC.

25 153. The compounds of claim 95 wherein MH is an arabinofuranosyl nucleoside.

154. The compounds of claim 153 wherein MH is selected from the group consisting of araA, araT, 5-propynyl-1-arabinosyluracil, araC, FaraA, 9-(arabinofuranosyl)-2,6-diaminopurine, and 9-(arabinofuranosyl)guanine.

5 155. The compounds of claim 154 wherein MH is selected from the group consisting of araA, araC, and FaraA.

156. The compounds of claim 95 wherein MH is a carbocyclic nucleoside.

10 157. The compounds of claim 156 wherein MH is selected from the group consisting of 5-yl-carbocyclic 2'deoxyguanosine, CDG, cyclobut A, cyclobut G, and BHCG.

158. The compounds of claim 157 wherein MH is selected from the group consisting of 5-yl-carbocyclic 2'deoxyguanosine, and cyclobut G.

15 159. The compounds of claim 95 wherein MH is a fluoro sugar nucleoside.

20 160. The compounds of claim 159 wherein MH is selected from the group consisting of FLT, FLG, FIAC, FIAU, FMAU, FEAU, dFdC, 9-(2'-deoxy-2'fluororibofuranosyl) 2,6-diaminopurine, and 9-(2'-deoxy 2'fluororibofuranosyl)guanine.

161. The compounds of claim 160 wherein MH is selected from the group consisting of L-FMAU, and dFdC.

25 162. The compounds of claim 95 wherein MH is a dioxolane nucleoside.

163. The compounds of claim 162 wherein MH is selected from the group consisting of DAPD, DXG, and FDOC.

30 164. The compounds of claim 163 wherein MH is selected from the group consisting of DAPD.

165. The compounds of claim 95 wherein MH is an L-nucleoside.

166. The compounds of claim 165 wherein MH is selected from the group consisting of L-ddC, L-FddC, L-d4C, L-Fd4C, 3TC, FTC, and L-FMAU.

5

167. The compounds of claim 166 wherein MH is selected from the group consisting of 3TC, FTC, and L-FMAU.

10

b6
b7C
b7D
b7E
b7F
b7G
b7H
b7I
b7J
b7K
b7L
b7M
b7N
b7O
b7P
b7Q
b7R
b7S
b7T
b7U
b7V
b7W
b7X
b7Y
b7Z
b7AA
b7AB
b7AC
b7AD
b7AE
b7AF
b7AG
b7AH
b7AI
b7AJ
b7AK
b7AL
b7AM
b7AN
b7AO
b7AP
b7AQ
b7AR
b7AS
b7AT
b7AU
b7AV
b7AW
b7AX
b7AY
b7AZ
b7BA
b7BB
b7BC
b7BD
b7BE
b7BF
b7BG
b7BH
b7BI
b7BJ
b7BK
b7BL
b7BM
b7BN
b7BO
b7BP
b7BQ
b7BR
b7BS
b7BT
b7BU
b7BV
b7BW
b7BX
b7BY
b7BZ
b7CA
b7CB
b7CC
b7CD
b7CE
b7CF
b7CG
b7CH
b7CI
b7CJ
b7CK
b7CL
b7CM
b7CN
b7CO
b7CP
b7CQ
b7CR
b7CS
b7CT
b7CU
b7CV
b7CW
b7CX
b7CY
b7CZ
b7DA
b7DB
b7DC
b7DD
b7DE
b7DF
b7DG
b7DH
b7DI
b7DJ
b7DK
b7DL
b7DM
b7DN
b7DO
b7DP
b7DQ
b7DR
b7DS
b7DT
b7DU
b7DV
b7DW
b7DX
b7DY
b7DZ
b7EA
b7EB
b7EC
b7ED
b7EE
b7EF
b7EG
b7EH
b7EI
b7EJ
b7EK
b7EL
b7EM
b7EN
b7EO
b7EP
b7EQ
b7ER
b7ES
b7ET
b7EU
b7EV
b7EW
b7EX
b7EY
b7EZ
b7FA
b7FB
b7FC
b7FD
b7FE
b7FF
b7FG
b7FH
b7FI
b7FJ
b7FK
b7FL
b7FM
b7FN
b7FO
b7FP
b7FQ
b7FR
b7FS
b7FT
b7FU
b7FV
b7FW
b7FX
b7FY
b7FZ
b7GA
b7GB
b7GC
b7GD
b7GE
b7GF
b7GG
b7GH
b7GI
b7GJ
b7GK
b7GL
b7GM
b7GN
b7GO
b7GP
b7GQ
b7GR
b7GS
b7GT
b7GU
b7GV
b7GW
b7GX
b7GY
b7GZ
b7HA
b7HB
b7HC
b7HD
b7HE
b7HF
b7HG
b7HH
b7HI
b7HJ
b7HK
b7HL
b7HM
b7HN
b7HO
b7HP
b7HQ
b7HR
b7HS
b7HT
b7HU
b7HV
b7HW
b7HX
b7HY
b7HZ
b7IA
b7IB
b7IC
b7ID
b7IE
b7IF
b7IG
b7IH
b7II
b7IJ
b7IK
b7IL
b7IM
b7IN
b7IO
b7IP
b7IQ
b7IR
b7IS
b7IT
b7IU
b7IV
b7IW
b7IX
b7IY
b7IZ
b7JA
b7JB
b7JC
b7JD
b7JE
b7JF
b7JG
b7JH
b7JI
b7JJ
b7JK
b7JL
b7JM
b7JN
b7JO
b7JP
b7JQ
b7JR
b7JS
b7JT
b7JU
b7JV
b7JW
b7JX
b7JY
b7JZ
b7KA
b7KB
b7KC
b7KD
b7KE
b7KF
b7KG
b7KH
b7KI
b7KJ
b7KK
b7KL
b7KM
b7KN
b7KO
b7KP
b7KQ
b7KR
b7KS
b7KT
b7KU
b7KV
b7KW
b7KX
b7KY
b7KZ
b7LA
b7LB
b7LC
b7LD
b7LE
b7LF
b7LG
b7LH
b7LI
b7LJ
b7LK
b7LL
b7LM
b7LN
b7LO
b7LP
b7LQ
b7LR
b7LS
b7LT
b7LU
b7LV
b7LW
b7LX
b7LY
b7LZ
b7MA
b7MB
b7MC
b7MD
b7ME
b7MF
b7MG
b7MH
b7MI
b7MJ
b7MK
b7ML
b7MN
b7MO
b7MP
b7MQ
b7MR
b7MS
b7MT
b7MU
b7MV
b7MW
b7MX
b7MY
b7MZ
b7NA
b7NB
b7NC
b7ND
b7NE
b7NF
b7NG
b7NH
b7NI
b7NJ
b7NK
b7NL
b7NM
b7NN
b7NO
b7NP
b7NQ
b7NR
b7NS
b7NT
b7NU
b7NV
b7NW
b7NX
b7NY
b7NZ
b7OA
b7OB
b7OC
b7OD
b7OE
b7OF
b7OG
b7OH
b7OI
b7OJ
b7OK
b7OL
b7OM
b7ON
b7OO
b7OP
b7OQ
b7OR
b7OS
b7OT
b7OU
b7OV
b7OW
b7OX
b7OY
b7OZ
b7PA
b7PB
b7PC
b7PD
b7PE
b7PF
b7PG
b7PH
b7PI
b7PJ
b7PK
b7PL
b7PM
b7PN
b7PO
b7PP
b7PQ
b7PR
b7PS
b7PT
b7PU
b7PV
b7PW
b7PX
b7PY
b7PZ
b7QA
b7QB
b7QC
b7QD
b7QE
b7QF
b7QG
b7QH
b7QI
b7QJ
b7QK
b7QL
b7QM
b7QN
b7QO
b7QP
b7QQ
b7QR
b7QS
b7QT
b7QU
b7QV
b7QW
b7QX
b7QY
b7QZ
b7RA
b7RB
b7RC
b7RD
b7RE
b7RF
b7RG
b7RH
b7RI
b7RJ
b7RK
b7RL
b7RM
b7RN
b7RO
b7RP
b7RQ
b7RR
b7RS
b7RT
b7RU
b7RV
b7RW
b7RX
b7RY
b7RZ
b7SA
b7SB
b7SC
b7SD
b7SE
b7SF
b7SG
b7SH
b7SI
b7SJ
b7SK
b7SL
b7SM
b7SN
b7SO
b7SP
b7SQ
b7SR
b7SS
b7ST
b7SU
b7SV
b7SW
b7SX
b7SY
b7SZ
b7TA
b7TB
b7TC
b7TD
b7TE
b7TF
b7TG
b7TH
b7TI
b7TJ
b7TK
b7TL
b7TM
b7TN
b7TO
b7TP
b7TQ
b7TR
b7TS
b7TT
b7TU
b7TV
b7TW
b7TX
b7TY
b7TZ
b7UA
b7UB
b7UC
b7UD
b7UE
b7UF
b7UG
b7UH
b7UI
b7UJ
b7UK
b7UL
b7UM
b7UN
b7UO
b7UP
b7UQ
b7UR
b7US
b7UT
b7UU
b7UV
b7UW
b7UX
b7UY
b7UZ
b7VA
b7VB
b7VC
b7VD
b7VE
b7VF
b7VG
b7VH
b7VI
b7VJ
b7VK
b7VL
b7VM
b7VN
b7VO
b7VP
b7VQ
b7VR
b7VS
b7VT
b7VU
b7VV
b7VW
b7VX
b7VY
b7VZ
b7WA
b7WB
b7WC
b7WD
b7WE
b7WF
b7WG
b7WH
b7WI
b7WJ
b7WK
b7WL
b7WM
b7WN
b7WO
b7WP
b7WQ
b7WR
b7WS
b7WT
b7WU
b7WV
b7WW
b7WX
b7WY
b7WZ
b7XA
b7XB
b7XC
b7XD
b7XE
b7XF
b7XG
b7XH
b7XI
b7XJ
b7XK
b7XL
b7XM
b7XN
b7XO
b7XP
b7XQ
b7XR
b7XS
b7XT
b7XU
b7XV
b7XW
b7XX
b7XY
b7XZ
b7YA
b7YB
b7YC
b7YD
b7YE
b7YF
b7YG
b7YH
b7YI
b7YJ
b7YK
b7YL
b7YM
b7YN
b7YO
b7YP
b7YQ
b7YR
b7YS
b7YT
b7YU
b7YV
b7YW
b7YX
b7YY
b7YZ
b7ZA
b7ZB
b7ZC
b7ZD
b7ZE
b7ZF
b7ZG
b7ZH
b7ZI
b7ZJ
b7ZK
b7ZL
b7ZM
b7ZN
b7ZO
b7ZP
b7ZQ
b7ZR
b7ZS
b7ZT
b7ZU
b7ZV
b7ZW
b7ZX
b7ZY
b7ZZ